

REMARKS

It is respectfully requested that this application be reconsidered in view of the following remarks and that all of the claims remaining be allowed.

Rejection Under 35 U.S.C. §103 (Paragraphs 2 and 3 of the Office Action)

The rejection of claims 21-34 and 42-43 under 35 U.S.C. §103 as allegedly unpatentable in view of Schmidt et al. (WO99/02728; “Schmidt” hereinafter) and Schultz et al. (U.S. Patent No. 6,268,146; “Schultz” hereinafter) is respectfully traversed for the reasons set forth below.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all the elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See, e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) (citing *KSR*). The Office Action does not meet either of these requirements, as discussed below.

Claim 21 of the present application is directed to a method of determining a nucleic acid sequence, said method comprising:

- (a) hybridizing a primer nucleic acid to a single stranded template nucleic acid;
- (b) extending said primer nucleic acid by at least one complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein said at least one complementary nucleotide includes a 3' cleavable tag;

- (c) cleaving said 3' cleavable tag from said extension product to produce a cleaved tag, not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence; and
- (d) detecting said cleaved tag away from said extension product to determine said nucleic acid sequence.

Thus, the method of claim 21 includes making an extension product using a single stranded template and a primer. The extension product contains a 3' cleavable tag, which is subsequently cleaved from the extension product, leaving the extension product still hybridized to the template. The cleaved tag is then detected.

The combination of Schmidt and Schultz does not teach or suggest all the claim elements of claim 21. For example, neither reference teaches or suggests “cleaving said 3' cleavable tag from said extension product to produce a cleaved tag, not bound to said at least one complementary nucleotide, and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence” (part (c) of claim 21). The Office Action admits that Schmidt does not disclose part (c). However, the Office Action alleges that Schultz does:

Shultz et al. disclose a method which is used to determine the presence or absence of a predetermined (known) nucleic acid target sequence in a nucleic acid sample (see column 5, lines 44-46). The sample is admixed with a depolymerizing amount of an enzyme whose activity is to release one or more nucleotides from the 3'-terminus of a hybridized nucleic acid probe (see column 5, lines 63-67). The released nucleotides are identifier nucleotides located in a 3'-terminal region (See column 5, lines 61-63). The identifier nucleotides are fluorescently labeled (see column 6, lines 12-15). The presence of released nucleotide is analyzed via mass spectrometry (see column 16, lines 51-52).

From this excerpt, it is clear that Shultz discloses cleaving one or more nucleotides with a depolymerizing enzyme, rather than cleaving a 3' tag from a 3'-terminal nucleotide as required by claim 21. After cleaving of the 3' tag in the method of claim 21, the extension product still includes the at least one complementary nucleotide (i.e., the nucleotide(s) added during primer extension), and it is still hybridized to the template. In contrast, the depolymerizing enzyme of Shultz would have cleaved the extension product by at least one nucleotide. In fact, Shultz further discloses:

The depolymerization reaction mixture is maintained under depolymerizing conditions for a time period sufficient to permit the enzyme to depolymerize hybridized nucleic acid and release identifier nucleotides therefrom to form a treated reaction mixture. (column 12, lines 25-29 of Shultz)

Thus, Shultz teaches depolymerizing the hybridized nucleic acid rather than cleaving the 3' tag while leaving the extension product (including the at least one complementary nucleotide) hybridized to the template. Since Shultz, like Schmidt, does not disclose part (c) of claim 21, it does not cure the deficiency of Schmidt. Accordingly, the combined references do not teach or suggest all the claim elements.

Furthermore, a person of ordinary skill in the art would not have been motivated to combine Schmidt with Shultz. The Office Action asserts:

One of ordinary skill in the art would have been motivated to apply a depolymerizing enzyme to release fluorescently labeled identifier nucleotides as taught by Shultz et al. (See column 12, lines 15-24) because by doing so nucleic acid hybrid can be detected with very high levels of sensitivity without the need for radiochemicals or electrophoresis (see column 7, lines 7-10). It would have been prima facie obvious to apply a depolymerizing enzyme to release a cleaved tag which is not bound to at least one complementary nucleotide.

Applicant disagrees. Schmidt specifically states “This invention further avoids problems associated with fluorescence based methods” (page 18, second paragraph of Schmidt). Therefore, the reference teaches away from the combination suggested by the Office Action. In addition, Schmidt teaches separating fragments of different lengths and

cleaving the fragments in a mass spectrometer for mass spectrometry analyses (see, e.g., abstract of Schmidt). If a depolymerizing enzyme of Shultz is used for the cleavage, it would not be fast enough to preserve the real-time nature of Schmidt's method.

Therefore, the rejection does not meet the requirements under 35 U.S.C. §103. Since all the pending claims recite cleaving a 3' cleavable tag, the rejection is not proper against any of the claims.

For at least the foregoing reasons, withdrawal of this rejection is respectfully requested.

Conclusions

For the reasons set forth above, Applicant submits that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (408) 553-3738.

Respectfully submitted,

By ____/Ping Hwung/____
Ping F. Hwung
Reg. No. 44,164
Attorney for Applicant

IP Administration
Agilent Technologies, Inc.
Legal Department, DL-429
P.O. Box 7599
Loveland, CO 80537-0599

Date: January 27, 2009
Phone: (408) 553-3738